

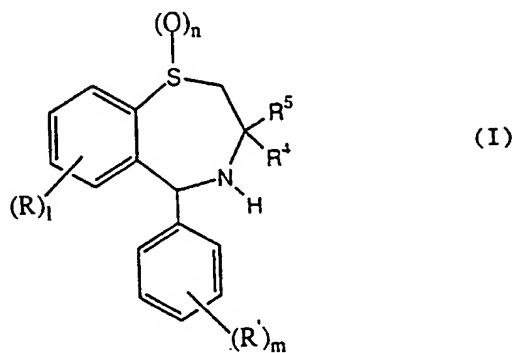


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(54) Title: HYPOLIPIDAEMIC BENZOTIAZEPINE COMPOUNDS



(57) Abstract

The present invention is concerned with compounds of formula (I) wherein 1 is an integer of from 0 to 4; m is an integer of from 0 to 5; n is an integer of from 0 to 2; R and R' are atoms or groups independently selected from halogen, nitro, phenylalkoxy, C₁₋₄ alkoxy, C₁₋₆ alkyl and -O(CH₂)_pSO₃R'' wherein p is an integer of from 1 to 4 and R'' is hydrogen or C₁₋₆ alkyl, wherein said phenylalkoxy, alkoxy and alkyl groups are optionally substituted by one or more halogen atoms; R⁴ is a C₁₋₆ straight alkyl group; and R⁵ is a C₂₋₆ straight alkyl group; and their salts, solvates and physiologically functional derivatives, with processes and novel intermediates for their preparation, with pharmaceutical compositions containing them and with their use in medicine, particularly in the prophylaxis and treatment of hyperlipidaemic conditions, such as atherosclerosis.

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Hypolipidaemic benzothiazepine compounds

The present invention is concerned with new hypolipidaemic compounds, with processes and novel intermediates for their preparation, with pharmaceutical compositions containing them and with their use in medicine, particularly in the prophylaxis and treatment of hyperlipidaemic conditions, such as atherosclerosis.

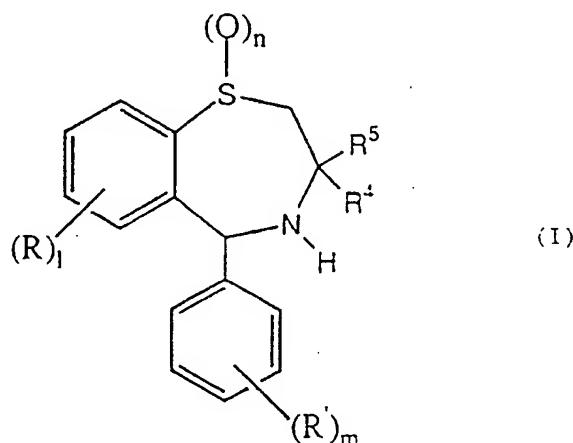
Hypolipidaemic conditions are often associated with elevated plasma concentrations of low density lipoprotein (LDL) cholesterol and very low density lipoprotein (VLDL) cholesterol. Such concentrations may be reduced by decreasing the absorption of bile acids from the intestine. One method by which this may be achieved is to inhibit the bile acid active uptake system in the terminal ileum. Such inhibition stimulates the conversion of cholesterol to bile acid by the liver and the resulting increase in demand for cholesterol produces a corresponding increase in the rate of clearance of LDL and VLDL cholesterol from the blood plasma or serum.

There has now been identified a novel class of heterocyclic compounds which reduce the plasma or serum concentrations of LDL and VLDL cholesterol and in consequence are particularly useful as hypolipidaemic agents. By decreasing the concentrations of cholesterol and cholesterol ester in the plasma, the compounds of the present invention retard the build-up of atherosclerotic lesions and reduce the incidence of coronary heart disease-related events. The latter are defined as cardiac events associated with increased concentrations of cholesterol and cholesterol ester in the plasma or serum.

For the purposes of this specification, a hyperlipidaemic condition is defined as any condition wherein the total cholesterol concentration (LDL + VLDL) in the plasma or serum is greater than 240mg/dL (6.21mmol/L) (J. Amer. Med. Assn. 256, 20. 2849-2858 (1986)).

USP 3,362,962 describes a genus of benzothiazepines outside the scope of the present invention which have muscle-relaxant and anticonvulsant activity; there is no disclosure in the patent specification that the compounds described therein may be useful as hypolipidaemic agents.

According to the present invention, there is provided a compound of formula (I)



wherein

l is an integer of from 0 to 4;

m is an integer of from 0 to 5;

n is an integer of from 0 to 2;

R and R' are atoms or groups independently selected from halogen, nitro, phenylalkoxy, C₁₋₄ alkoxy, C₁₋₆ alkyl and -O(CH₂)_pSO₃R" wherein p is an integer of from 1 to 4 and R" is hydrogen or C₁₋₆ alkyl, wherein said phenylalkoxy, alkoxy and alkyl groups are optionally substituted by one or more halogen atoms;

R⁴ is a C₁₋₆ straight, that is, unbranched, alkyl group; and

R⁵ is a C₂₋₆ straight, that is, unbranched, alkyl group;

and salts, solvates and physiologically functional derivatives thereof.

Pharmaceutically acceptable salts are particularly suitable for medical applications because of their greater aqueous solubility relative to the parent, ie basic, compounds. Such salts must clearly have a pharmaceutically acceptable anion or cation. Suitable pharmaceutically acceptable acid addition salts of the compounds of the present invention include those derived from inorganic acids, such as hydrochloric, hydrobromic, phosphoric, metaphosphoric, nitric, sulphonic and sulphuric acids, and organic acids, such as acetic, benzenesulphonic, benzoic, citric, ethanesulphonic, fumaric, gluconic, glycollic, isothionic, lactic, lactobionic, maleic, malic, methanesulphonic, succinic, p-toluenesulphonic, tartaric and trifluoroacetic acids. The chloride salt is particularly preferred for medical purposes. Suitable pharmaceutically acceptable base salts include ammonium salts, alkali metal salts, such as sodium and potassium salts, and alkaline earth salts, such as magnesium and calcium salts.

Salts having a non-pharmaceutically acceptable anion are within the scope of the invention as useful intermediates for the preparation or purification of pharmaceutically acceptable salts and/or for use in non-therapeutic, for example, in vitro, applications.

The term "physiologically functional derivative" as used herein refers to any physiologically acceptable derivative of a compound of the present invention, for example, an ester, which upon administration to a mammal, such as a human, is capable of providing (directly or indirectly) such a compound or an active metabolite thereof.

A further aspect of the present invention is prodrugs of the compounds of the invention. Such prodrugs can be metabolised in vivo to give a compound according to the invention. These prodrugs may or may not be active in their own right.

The compounds of the present invention can also exist in different polymorphic forms, for example, amorphous and crystalline polymorphic forms. All polymorphic forms of the compounds of the present invention are within the scope of the invention and are a further aspect thereof.

The term "alkyl" as used herein refers, unless otherwise stated, to a monovalent straight or branched chain radical. Likewise, the term "alkoxy" refers to a monovalent straight or branched chain radical attached to the parent molecular moiety through an oxygen atom. The term "phenylalkoxy" refers to a monovalent phenyl group attached to a divalent C_{1-6} alkylene group which is itself attached to the parent molecular moiety through an oxygen atom.

The compounds of formula (I) may exist in forms wherein one or both of the carbon centres $-C(R^4)(R^5)-$ and $-CHPh(R')_m-$ (wherein Ph is the phenyl group) is/are chiral. The present invention includes within its scope each possible optical isomer substantially free, ie associated with less than 5% of any other optical isomer(s), and mixtures of one or more optical isomers in any proportions, including racemic mixtures.

For the purposes of this specification, the absolute chiralities of the aforementioned carbon centres are given in the order $-C(R^4)(R^5)-$, then $-CHPh(R')_m-$. For example, the prefix "(RS)-" denotes an (R)-configuration at $-C(R^4)(R^5)-$ and an (S)-configuration at $-CHPh(R')_m-$ and the prefix "(RS,SR)-" denotes a mixture of two isomers wherein one is (R)- at $-C(R^4)(R^5)-$ and (S)- at $-CHPh(R')_m-$ and the other is (S)- at $-C(R^4)(R^5)-$ and (R)- at $-CHPh(R')_m-$. Other permutations will be clear to the skilled person.

In those cases where the absolute stereochemistry at $-C(R^4)(R^5)-$ and $-CHPh(R')_m-$ has not been determined, the compounds of the invention are defined in terms of the relative positions of the R^4/R^5 and $H/Ph(R')_m$ substituents. Thus those compounds wherein the bulkier

of the R^4 and R^5 substituents, ie the substituent of higher mass, and the $Ph(R')_m$ substituent are both located on the same side of the thiazepine ring are referred to herein as "cis", and those compounds in which they are located on opposite sides of the ring are referred to as "trans". It will be evident to a skilled person that both "cis" and "trans" compounds of the invention can each exist in two enantiomeric forms which are individually designated "(+)-" or "(-)-" according to the direction of rotation of a plane of polarised light when passed through a sample of the compound. Cis or trans compounds of the invention in which the individual enantiomers have not been resolved are referred to herein using the prefix "(+-)-".

Preferred compounds of formula (I) having particularly desirable hypolipidaemic properties include those wherein

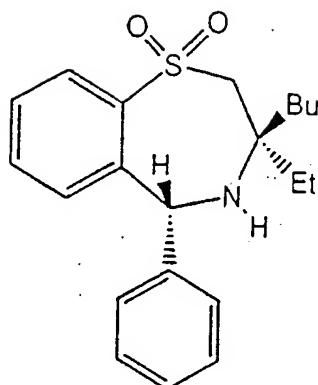
n is 2;

R^4 is methyl, ethyl, n-propyl, or n-butyl; and/or

R^5 is ethyl, n-propyl, or n-butyl.

Of these, the (RR)-, (SS)- and (RR,SS)-trans compounds are particularly preferred.

A compound of formula (I) having exceptional hypolipidaemic properties is trans-3-butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide in both its (RR)- and (RR,SS)-forms, viz (--)-(RR)-3-butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide and (+)-trans-3-butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide respectively. The former is especially preferred and is depicted thus:



According to further aspects of the invention, there are also provided:

- (a) compounds of formula (I) and pharmaceutically acceptable salts, solvates and physiologically functional derivatives thereof for use as therapeutic agents, particularly in the prophylaxis and treatment of clinical conditions for which a bile acid uptake inhibitor is indicated, for example, a hyperlipidaemic condition, such as atherosclerosis;
- (b) pharmaceutical compositions comprising a compound of formula (I) or one of its pharmaceutically acceptable salts, solvates, or physiologically functional derivatives, at least one pharmaceutically acceptable carrier and, optionally, one or more other physiologically active agents;
- (c) the use of a compound of formula (I) or of a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition for which a bile acid uptake inhibitor is indicated, for example, a hyperlipidaemic condition, such as atherosclerosis;
- (d) a method of inhibiting the absorption of bile acids from the intestine of a mammal, such as a human, which comprises

administering an effective bile acid absorption inhibiting amount of a compound of formula (I) or of a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof to the mammal;

- (e) a method of reducing the blood plasma or serum concentrations of LDL and VLDL cholesterol in a mammal, such as a human, which comprises administering an effective cholesterol reducing amount of a compound of formula (I) or of a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof to the mammal;
- (f) a method of reducing the concentrations of cholesterol and cholesterol ester in the blood plasma or serum of a mammal, such as a human, which comprises administering an effective cholesterol and cholesterol ester reducing amount of a compound of formula (I) or of a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof to the mammal;
- (g) a method of increasing the faecal excretion of bile acids in a mammal, such as a human, which comprises administering an effective bile acid faecal excretion increasing amount of a compound of formula (I) or of a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof to the mammal;
- (h) a method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a bile acid uptake inhibitor is indicated, for example, a hyperlipidaemic condition, such as atherosclerosis, which comprises administering a therapeutically effective amount of a compound of the formula (I) or of a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof to the mammal;

- (i) a method of reducing the incidence of coronary heart disease-related events in a mammal, such as a human, which comprises administering an effective coronary heart disease-related events reducing amount of a compound of formula (I) or of a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof;
- (j) a method of reducing the concentration of cholesterol in the blood plasma or serum of a mammal, such as a human, which comprises administering an effective cholesterol reducing amount of a compound of formula (I);
- (k) processes for the preparation of compounds of formula (I) (including salts, solvates and physiologically functional derivatives thereof as defined herein); and
- (l) compounds of formula (II) for use as intermediates in the preparation of compounds of formula (I).

Hereinafter all references to "compound(s) of formula (I)" refer to compound(s) of formula (I) as described above together with their salts, solvates and physiologically functional derivatives as defined herein.

The amount of a compound of formula (I) which is required to achieve the desired biological effect will, of course, depend on a number of factors, for example, the specific compound chosen, the use for which it is intended, the mode of administration and the clinical condition of the recipient. In general, a daily dose is in the range of from 0.3mg to 100mg (typically from 3mg to 50mg) per day per kilogram bodyweight, for example, 3-10mg/kg/day. An intravenous dose can, for example, be in the range of from 0.3mg to 1.0mg/kg, which can conveniently be administered as an infusion of from 10ng to 100ng per kilogram per minute. Infusion fluids suitable for this purpose can

contain, for example, from 0.1ng to 10mg, typically from 1ng to 10mg, per millilitre. Unit doses can contain, for example, from 1mg to 10g of the active compound. Thus ampoules for injection can contain, for example, from 1mg to 100mg and orally administrable unit dose formulations, such as tablets or capsules, may contain, for example, from 1.0 to 1000mg, typically from 10 to 600mg. In the case of pharmaceutically acceptable salts, the weights indicated above refer to the weight of the benzothiazepine ion derived from the salt.

For the prophylaxis or treatment of the conditions referred to above, the compounds of formula (I) can be used as the compound per se, but are preferably presented with an acceptable carrier in the form of a pharmaceutical composition. The carrier must, of course, be acceptable in the sense of being compatible with the other ingredients of the composition and must not be deleterious to the recipient. The carrier can be a solid or a liquid, or both, and is preferably formulated with the compound as a unit-dose composition, for example, a tablet, which can contain from 0.05% to 95% by weight of the active compound. Other pharmacologically active substances can also be present including other compounds of formula (I). The pharmaceutical compositions of the invention can be prepared by any of the well known techniques of pharmacy consisting essentially of admixing the components.

Pharmaceutical compositions according to the present invention include those suitable for oral, rectal, topical, buccal (e.g. sub-lingual) and parenteral (e.g. subcutaneous, intramuscular, intradermal, or intravenous) administration, although the most suitable route in any given case will depend on the nature and severity of the condition being treated and on the nature of the particular compound of formula (I) which is being used. Enteric-coated and enteric-coated controlled release formulations are also within the scope of the invention. Suitable enteric coatings include cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropylmethylcellulose phthalate and

anionic polymers of methacrylic acid and methacrylic acid methyl ester.

Pharmaceutical compositions suitable for oral administration can be presented in discrete units, such as capsules, cachets, lozenges, or tablets, each containing a predetermined amount of a compound of formula (I); as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. As indicated, such compositions can be prepared by any suitable method of pharmacy which includes the step of bringing into association the active compound and the carrier (which can constitute one or more accessory ingredients). In general, the compositions are prepared by uniformly and intimately admixing the active compound with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the product. For example, a tablet can be prepared by compressing or moulding a powder or granules of the compound, optionally with one or more accessory ingredients. Compressed tablets can be prepared by compressing, in a suitable machine, the compound in a free-flowing form, such as a powder or granules optionally mixed with a binder, lubricant, inert diluent and/or surface active/dispersing agent(s). Moulded tablets can be made by moulding, in a suitable machine, the powdered compound moistened with an inert liquid diluent.

Pharmaceutical compositions suitable for buccal (sub-lingual) administration include lozenges comprising a compound of formula (I) in a flavoured base, usually sucrose and acacia or tragacanth, and pastilles comprising the compound in an inert base such as gelatin and glycerin or sucrose and acacia.

Pharmaceutical compositions suitable for parenteral administration conveniently comprise sterile aqueous preparations of a compound of formula (I), preferably isotonic with the blood of the intended recipient. These preparations are preferably administered intravenously, although administration can also be effected by means

of subcutaneous, intramuscular, or intradermal injection. Such preparations can conveniently be prepared by admixing the compound with water and rendering the resulting solution sterile and isotonic with the blood. Injectable compositions according to the invention will generally contain from 0.1 to 5% w/w of the active compound.

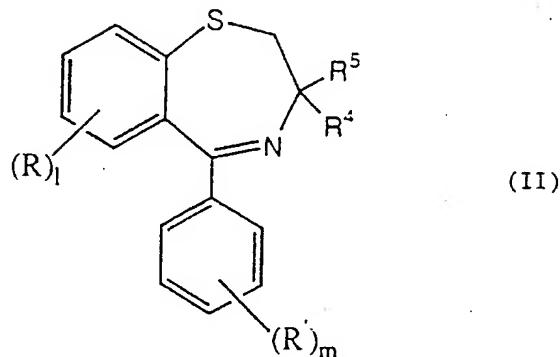
Pharmaceutical compositions suitable for rectal administration are preferably presented as unit-dose suppositories. These can be prepared by admixing a compound of formula (I) with one or more conventional solid carriers, for example, cocoa butter, and then shaping the resulting mixture.

Pharmaceutical compositions suitable for topical application to the skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which can be used include vaseline, lanoline, polyethylene glycols, alcohols, and combinations of two or more thereof. The active compound is generally present at a concentration of from 0.1 to 15% w/w of the composition, for example, from 0.5 to 2%.

Transdermal administration is also possible. Pharmaceutical compositions suitable for transdermal administration can be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Such patches suitably contain the active compound in an optionally buffered, aqueous solution, dissolved and/or dispersed in an adhesive, or dispersed in a polymer. A suitable concentration of the active compound is about 1% to 35%, preferably about 3% to 15%. As one particular possibility, the active compound can be delivered from the patch by electrotransport or iontophoresis, for example, as described in Pharmaceutical Research, 3(6), 318 (1986).

The compounds of the invention can be prepared by conventional methods known to a skilled person or in an analogous manner to processes described in the art.

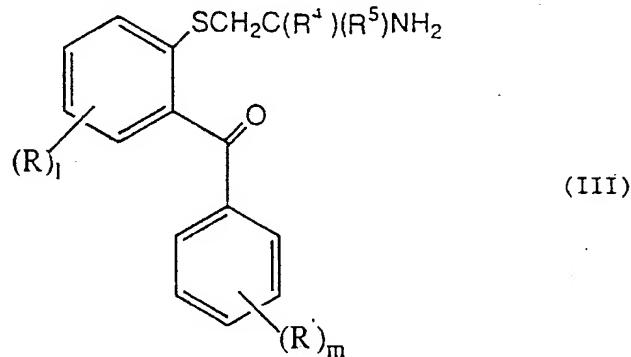
For example, compounds of formula (I) wherein $n = 0$ can be prepared by reducing the imine bond of a compound of formula (II)



wherein l , m , R , R' , R^4 and R^5 are as hereinbefore defined, using, for example, a boron compound, such as borane, in a suitable solvent, such as THF, or catalytic hydrogenation using, for example, a palladium catalyst, such as 10% Pd/C.

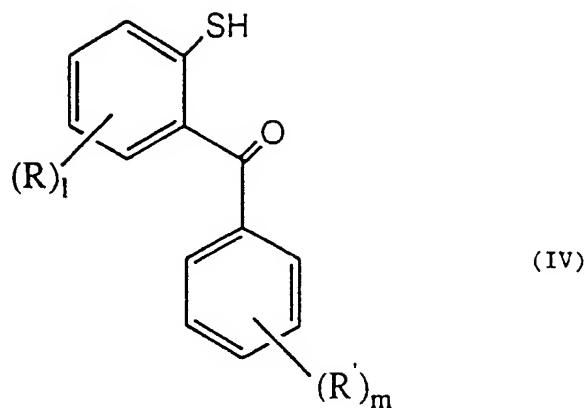
Compounds of formula (II) as herein defined are considered to be novel and constitute a further aspect of the present invention.

Compounds of formula (II) can be prepared by cyclising compounds of formula (III)

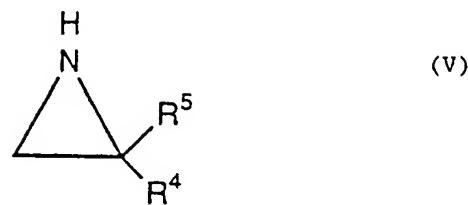


wherein l , m , R , R' , R^4 and R^5 are as hereinbefore defined, by, for example, azeotropic distillation or refluxing in the presence of a suitable drying agent, such as molecular sieves, in a suitable solvent, for example, 2,6-lutidine, in the presence of an acid, such as HCl.

Compounds of formula (III) can be prepared by reacting a compound of formula (IV)

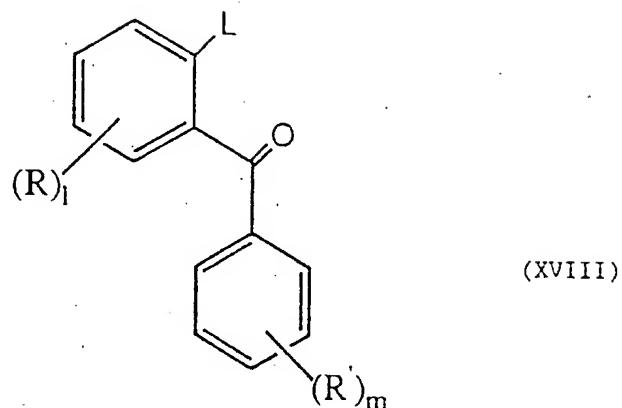


wherein l, m, R and R' are as hereinbefore defined, with a compound of formula (V)



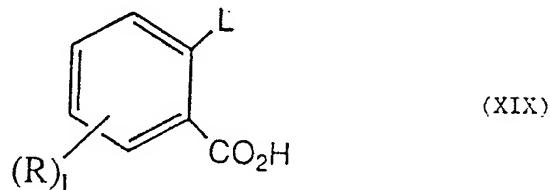
wherein R⁴ and R⁵ are as hereinbefore defined, typically in a polar solvent, for example, methanol.

Compounds of formula (III) can also be prepared by reacting a compound of formula (XVIII)



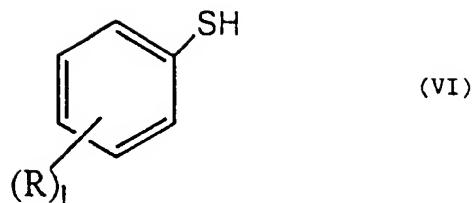
wherein 1, m, R and R' are as hereinbefore defined and L is a suitable leaving group, for example, halogen, with a compound of formula $\text{HSCH}_2\text{C}(\text{R}^4)(\text{R}^5)\text{NH}_2$ wherein R^4 and R^5 are as hereinbefore defined.

Compounds of formula (XVIII) can be prepared by reacting a compound of formula (XIX)



wherein 1, L and R are as hereinbefore defined, with a compound of formula $\text{Ph}(\text{R}')_m\text{H}$ wherein Ph is a phenyl group and m and R' are as hereinbefore defined, typically by a Friedel-Crafts reaction using, for example, aluminium chloride.

Compounds of formula (IV) can be prepared by reacting a compound of formula (VI)

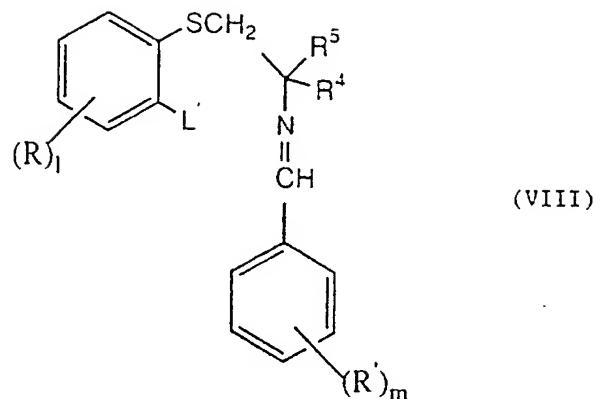


wherein l and R are as hereinbefore defined, with a compound of formula $(R')_m PhCN$ wherein Ph is a phenyl group and m and R' are as hereinbefore defined. The reaction is typically carried out by lithiation of compound (VI) using, for example, n -butyl lithium in the presence of N,N,N',N' -tetramethylethylenediamine (TMEDA) followed by reaction with the appropriate benzonitrile in a non-polar solvent, for example, cyclohexane.

Compounds of formula (IV) can also be prepared by reacting a compound of formula (XVIII) as hereinbefore defined with sodium sulphide.

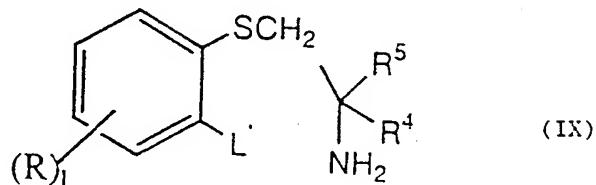
Compounds of formulae (V), (XIX), (VI) and $(R')_m PhCN$ as hereinbefore defined can be obtained commercially or prepared by methods known to those skilled in the art or obtainable from the chemical literature. Thus compounds of formula (V) can be prepared from the corresponding 2-substituted 2-aminoethanols.

Compounds of formula (I) wherein $n = 0$ can also be prepared by cyclising a compound of formula (VIII)



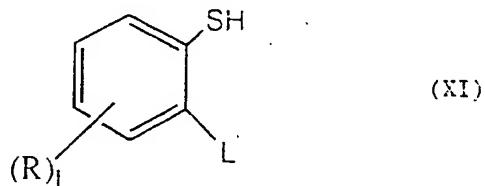
wherein 1, m, R, R', R⁴ and R⁵ are as hereinbefore defined and L' is halogen, for example, bromine, by treatment with strong base, for example, n-butyl lithium, in a suitable solvent, such as THF, at a low temperature, for example, -78°C.

Compounds of formula (VIII) can be prepared by reaction of a compound of formula (IX)



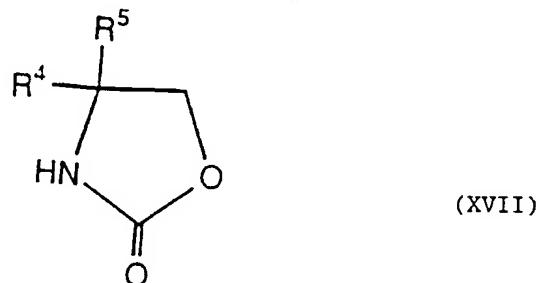
wherein 1, L', R, R⁴ and R⁵ are as hereinbefore defined, with a compound of formula (R')_mPhCHO wherein Ph is a phenyl group and m and R' are as hereinbefore defined. The reaction is typically carried out in a non-polar solvent, for example, toluene, in the presence of an acid, such as p-toluenesulphonic acid.

Compounds of formula (IX) can be prepared by reacting a compound of formula (XI)



wherein l , L' and R are as hereinbefore defined, with a compound of formula (V) wherein R^4 and R^5 are as hereinbefore defined, typically in a polar solvent, such as methanol.

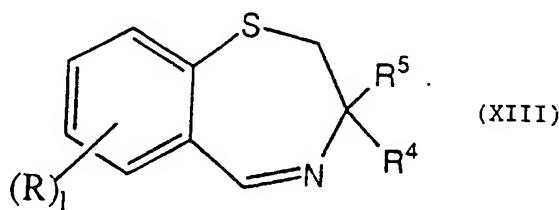
Compounds of formula (IX) can also be prepared by reacting a compound of formula (XI) as hereinbefore defined with a compound of formula (XVII)



wherein R^4 and R^5 are as hereinbefore defined, in the presence of a Lewis acid, for example, lithium chloride, at an elevated temperature, such as $170\text{--}210^\circ\text{C}$.

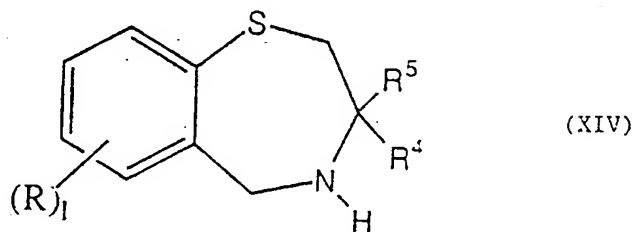
Compounds of formulae $(R')_m\text{PhCHO}$ as hereinbefore defined, (XI) and (XVII) can be obtained commercially or prepared by methods known to those skilled in the art or obtainable from the chemical literature. Thus compounds of formula (XI) may be prepared from the corresponding disulphides and compounds of formula (XVII) from the corresponding 2-substituted 2-aminoethanols.

Compounds of formula (I) wherein $n = 0$ can also be obtained by phenylating a compound of formula (XIII)



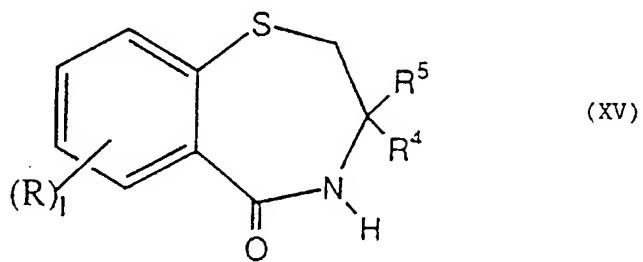
wherein 1, R, R⁴ and R⁵ are as hereinbefore defined, using, for example, an organometallic compound, such as (R')_mPhLi, (R')_mPhCu, (R')_mPhZn, or (R')_mPhMgBr wherein Ph is a phenyl group and m and R' are as hereinbefore defined.

Compounds of formula (XIII) can be prepared by dehydrogenating the corresponding compound of formula (XIV)



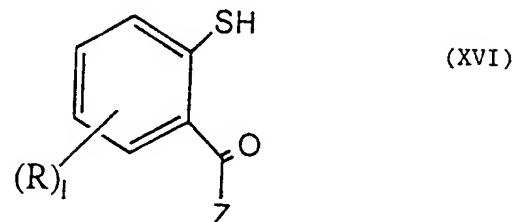
wherein 1, R, R⁴ and R⁵ are as hereinbefore defined, using, for example, an oxidising agent, such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), in a suitable solvent, for example, toluene.

Compounds of formula (XIV) can be prepared by reducing the amide carbonyl group of the corresponding compound of formula (XV)



wherein 1, R, R⁴ and R⁵ are as hereinbefore defined, using, for example, lithium aluminium hydride.

Compounds of formula (XV) can be prepared by reacting a compound of formula (XVI)



wherein 1 and R are as hereinbefore defined and Z is C_{1-4} alkoxy, for example, methoxy, with a compound of formula (V) wherein R^4 and R^5 are as hereinbefore defined.

The compound of formula (XVI) wherein 1 = 0 can be prepared from commercially available 2,2'-dithiosalicylic acid by methods known to those skilled in the art. Compounds of formula (XVI) wherein 1 ≠ 0 can be obtained commercially or prepared by methods known to those skilled in the art or obtainable from the chemical literature.

Compounds of formula (I) wherein n = 1 or 2 can be prepared by oxidation of the corresponding compound of formula (I) wherein n = 0 or by oxidation of the corresponding compound of formula (III) wherein n = 0 prior to cyclisation and reduction to the compound of formula (I) using suitable oxidation conditions, for example, in the case where n is to be 2, 30% aqu. H_2O_2 in the presence of trifluoroacetic acid.

Individual optical isomers of compounds of formula (I) substantially free, of other optical isomers can be obtained either by chiral synthesis, for example, by the use of the appropriate chiral starting material(s), such as the aziridine (V), or by resolution of the products obtained from achiral syntheses, for example, by chiral hplc.

Optional conversion of a compound of formula (I) to a corresponding acid addition salt may be effected by reaction with a solution of the appropriate acid, for example, one of those recited earlier. Optional

conversion to a corresponding base salt may be effected by reaction with a solution of the appropriate base, for example, sodium hydroxide. Optional conversion to a physiologically functional derivative, such as an ester, can be carried out by methods known to those skilled in the art or obtainable from the chemical literature.

For a better understanding of the invention, the following Examples are given by way of illustration and are not to be construed in any way as limiting the scope of the invention.

Synthetic Example 1

Preparation of (--)-(RR)-3-butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide

(a) Ethyl 2-aminobutyrate hydrochloride

A slurry of 2-aminobutyric acid (100g, Aldrich) in absolute ethanol (300ml) was stirred under nitrogen at 0°C and thionyl chloride (120.79g) was added dropwise. The reaction was stirred overnight at 0°C and then gradually warmed to room temperature. The resulting white slurry was heated under reflux for 3 hours, left to cool for 10 minutes, then poured into chilled diethyl ether (600ml) with hand stirring. The suspension was filtered and the solid product dried to give the desired product (150g) as a white solid. ¹H NMR consistent with proposed structure.

(b) Ethyl 2-benzylideneaminobutyrate

A solution of the product from step (a) (149.57g), magnesium sulphate (74.32g), and triethylamine (246ml) in dichloromethane (1500ml) was stirred at room temperature under nitrogen and benzaldehyde (94.91g, Aldrich) was added dropwise. The mixture was stirred at room temperature for 3 hours then filtered. The filtrate was concentrated, triturated in diethyl ether, filtered

and concentrated to yield the desired product as a yellow oil (174g). ^1H NMR consistent with the proposed structure.

(c) Ethyl 2-benzylideneamino-2-ethylhexanoate

Sodium hydride (32.49g, 60% dispersion in oil) and N,N-Dimethyl-formamide (DMF) (700ml) were stirred under nitrogen at room temperature and a solution of the product from (b) (178.13g) in DMF was added dropwise. After 2 hours stirring at room temperature, a solution of butyl iodide (149.48g) in DMF was added dropwise and the reaction left stirring for a further 2 hours. The reaction was poured into an ice cold mixture of water (560ml), diethyl ether (300ml) and ammonium chloride (120g). The resulting organic layer was dried over potassium carbonate then concentrated to give the desired product as a brown oil (220g).

(d) Ethyl 2-amino-2-ethylhexanoate

The product from (c) (233.02g) was partitioned between petroleum ether and 10% w/w hydrochloric acid (421ml) and stirred at room temperature for 2 hours. The aqueous layer was extracted twice with petroleum ether and then chilled with ethyl acetate in an ice-salt bath. Sodium hydroxide pellets were added to the mixture until the aqueous layer was at pH 10. The latter was extracted twice with ethyl acetate and the combined ethyl acetate layers were dried over potassium carbonate, then concentrated and vacuum distilled to give the desired product as a colourless oil. ^1H NMR consistent with the proposed structure.

(e) 2-Amino-2-ethylhexan-1-ol

Lithium aluminium hydride (22.22g) was added to anhydrous diethyl ether (450ml) under nitrogen. The product from (d) (129.0g) was diluted with diethyl ether (40ml) and added dropwise. The reaction was refluxed for 1 hour then cooled to room temperature.

1M sodium hydroxide (23ml) was added dropwise followed by deionised water. The resulting suspension was filtered and the filtrate concentrated to give the desired product as a colourless oil (87.9g). ^1H NMR consistent with the proposed structure.

(f) 2-Butyl-2-ethylaziridine

Acetonitrile (150ml) and the product from (e) (20.0g) were mixed under nitrogen, cooled to 2-3°C and chlorosulphonic acid (16.04g, Aldrich) was added dropwise keeping the temperature below 10°C. The coolant was removed and the slurry left to stir for 80 minutes at room temperature. The reaction was concentrated in vacuo and co-distilled with water (50ml). 50% Aqueous sodium hydroxide (55.2g) and water (50ml) were added and the mixture was distilled at atmospheric pressure. The organic layer was collected from the distillate and dried with solid potassium hydroxide to give the desired product (12.8g). ^1H NMR consistent with proposed structure.

(g) 2-Thiobenzophenone

A solution of N,N,N',N'-tetramethylethylenediamine (TMEDA) (104.6g) in cyclohexane (500ml) was cooled and 2.5M *n*-butyl lithium (360ml) was added. A solution of thiophenol (50.0g) in cyclohexane (100ml) was added slowly to the butyl lithium solution and the reaction was stirred at room temperature overnight. Benzonitrile (46.4g, Aldrich) in cyclohexane (100ml) was added to give a slurry which was stirred overnight at room temperature. Water (500ml) was added and the mixture stirred for 30 minutes then the aqueous layer was separated and treated with solid sodium hydroxide to give pH 14. The solution was boiled for 90 minutes, cooled to room temperature and acidified to pH 1-2 with conc. HCl. The acidic solution was extracted with dichloromethane and the combined extracts dried, then concentrated to give a red oil. The oil was treated with 1M aqu.

NaOH, extracted with dichloromethane and the aqueous layer separated and treated with conc. HCl acid to give an oil. The oil was extracted into dichloromethane and the combined extracts dried, then concentrated to give the desired product as an orange-red oil (83.4g). ^1H NMR consistent with proposed structure.

(h) 2-(2-Amino-2-ethylhexylthio)benzophenone

The product from (g) was dissolved in methanol (to a total volume of 250ml) and an equimolar amount of the product from (f) in methanol (total volume 120ml) was added over 20 minutes. The mixture was stirred at room temperature for 75 minutes then concentrated in vacuo to give a dark red oil. This oil was taken up in diethyl ether (400ml) and filtered to remove contaminating solids. The desired product was left as a solution in ether for use in (i). ^1H NMR consistent with proposed structure.

(i) 3-Ethyl-3-butyl-5-phenyl-2,3-dihydrobenzothiazepine

1M Ethereal hydrochloric acid (275ml) was added to a solution of the product from (h) (85.0g) in diethyl ether and the mixture was concentrated in vacuo. The residue was azeotropically distilled by addition of 2,6-lutidine (175ml) and refluxing in a Dean-Stark apparatus overnight. The mixture was concentrated in vacuo, neutralised by addition of 5% sodium bicarbonate then the minimum volume of ethyl acetate was added to dissolve the red oil. The organic layer was separated, washed with brine, dried and concentrated. The crude residue was purified by column chromatography on silica using toluene as eluant. Concentration of the relevant fractions gave the desired product (63.7g). ^1H NMR consistent with the proposed structure.

(j) (+)-Trans-3-butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine

1M Diborane (211ml in THF) was added over 45 minutes to a solution of the product from (i) (63.7g) in THF under nitrogen. Reaction was stirred at room temperature for 17 hours. 50% Hydrochloric acid (125ml) was added and the mixture was concentrated in vacuo. The residue was partitioned between aqu. NaOH and ethyl acetate. The organic layer was dried and concentrated to give an orange-yellow oil (67.5g) comprising cis and trans isomers which was chromatographed on silica using toluene as eluant to give the desired product as a pale yellow oil (27.3g). ^1H NMR consistent with the proposed structure.

(k) (+)-Trans-3-butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide

30% Aqueous hydrogen peroxide (73.1g) and trifluoroacetic acid (TFA) (225ml) were cooled and a solution of the product from (j) (70.0g) in TFA (200ml) was added. The reaction was stirred at room temperature for 24 hours, then added to water (1000ml) and basified with solid sodium hydroxide. The resulting insoluble solid was filtered off, warmed with 1M aqu. NaOH and extracted into ethyl acetate. The combined extracts were evaporated in vacuo to give the desired product (69.0g). ^1H NMR consistent with the proposed structure.

(l) (-)-(RR)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide

The product from (k) (208.3g) was mixed with diethyl ether (1500ml) and (-)-di-p-toluoyl-L-tartaric acid (225.2g, Schweitzerhall) in diethyl ether added. On standing, a white solid precipitated which was filtered off and recrystallised from acetone/hexane to give the desired product as the acid salt. The

title compound was liberated from its salt by treatment with 1M aqu. NaOH and extracted with ethyl acetate. The combined extracts were evaporated in vacuo to give the desired product as a white solid (83.0g), mp 115-116°C.

Analysis: Calcd. C 70.55; H 7.61; N 3.92; S 8.97

Found: C 70.58; H 7.56; N 3.96; S 8.88

¹H NMR (DMSO-d₆), δ: 0.81-0.92 (6H, m, 2xCH₃); 1.15-1.40 (4H, m, 2xCH₂); 1.47-1.70 (3H, m, CH₂ + NH); 1.80-1.90 (1H, m, CH₂); 2.13-2.24 (1H, m, CH₂); 3.07-3.46 (2H, q, CH₂SO₂); 6.09 (1H, s, CH); 6.71-6.74 (1H, m, Ar-H); 7.26-7.41 (7H, m, Ar-H); 8.10-8.13 (1H, m, Ar-H)

Alternative preparation of (-)-(RR)-3-butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide

(a) Ethyl 2-aminobutyrate hydrochloride

Thionyl chloride (1.25 moles) was added to a solution of 2-aminobutyric acid (1 mole) in SD12A3 (95% ethanol/5% toluene) at a temperature of <5°C. When addition was complete, the mixture was stirred at 27°C for 16 hours and the resulting precipitate filtered off and washed with methyl *t*-butyl ether to give the desired product as a white solid (97% yield).

(b) Ethyl 2-benzylideneaminobutyrate

Triethylamine (2 moles) was added to a solution of the product from step (a) (1 mole) in toluene. When addition was complete, benzaldehyde (1 mole) was added. The mixture was azeotroped until no further water was collected, then cooled to room temperature and filtered. The filtrate was evaporated in vacuo to give the desired product as an oil.

(c) Ethyl 2-benzylideneamino-2-ethylhexanoate

A 1.6M solution of *n*-butyl lithium in hexane (33 mmoles, Aldrich) was added to a solution of diisopropylamine (40 mmoles) in THF (21ml) at a temperature of 5-10°C. When addition was complete, the mixture was added to a solution of the product from step (b) (30 mmoles) in THF (20ml) at a temperature of 5-10°C. When addition was complete, *n*-butyl iodide (40 mmoles) was added and the mixture allowed to warm to room temperature. After 20 hours, the mixture was poured into water/diethyl ether (1.1L/0.5L) and the organic layer separated, washed with brine (1.1L), dried and evaporated in vacuo to give the desired product as an amber liquid (100% yield).

(d) Ethyl 2-amino-2-ethylhexanoate

A solution of the product from step (c) (1 mole) in 1N aqu. HCl (1.2 moles) was stirred for 10 minutes at room temperature, then washed with toluene. The pH of the remaining aqueous phase was adjusted to 7 using 12.5% w/v sodium hydroxide, then cooled to 10°C, further basified to pH 12 and extracted with toluene. The extracts were combined, washed with brine, dried and evaporated in vacuo. The residue was distilled to give the desired product as an oil (70-80% yield).

(e) (R)-2-Amino-2-ethylhexanoic acid

A suspension of pig liver esterase (0.1g, Sigma-Aldrich-Fluka) in water was added to an aqueous solution of the product from step (d) (100g). When addition was complete, the pH of the mixture was adjusted to 9.7 using 1N aqu. NaOH and maintained at this value by the addition of further 1N aqu. NaOH. After the addition of a predetermined amount of 1N aqu. NaOH (85g over 10 hours), the mixture was washed with diethyl ether to remove unreacted (S)-ethyl 2-amino-2-ethyl-hexanoate. The remaining

aqueous phase was evaporated in vacuo to give a white solid comprising the desired product and its sodium salt (40-45% yield).

(f) (R)-2-Amino-2-ethylhexan-1-ol

The product from step (e) (20g) was added to a 1M solution of lithium aluminium hydride (1.5 molar equivalents) in THF and the mixture refluxed for 3 hours, then stirred for 16 hours at room temperature. The mixture was cooled to about 0°C, then quenched with water and 1N aqu. NaOH added. The resulting solid was broken up with additional water and the suspension heated at 50°C for 5 minutes, then cooled to room temperature, diethyl ether (100ml) added and filtered. The filtrate was evaporated in vacuo to give the desired product as an oil (82% yield).

(g) (R)-2-Butyl-2-ethylaziridine

Chlorosulphonic acid (1 molar equivalent) was added to a solution of the product from step (f) (15g) in dichloroethane (90ml) at a temperature of <16°C. When addition was complete, the mixture was stirred for 2 hours at room temperature and then evaporated in vacuo. Water (60ml) and 50% w/v aqu. NaOH (41ml) were added and the mixture distilled at atmospheric pressure. The organic phase of the distillate was separated and dried over KOH to give a solution of the desired product (77% yield).

(h) 2-Thiobenzophenone

A 2.5M solution of n-butyl lithium (2 moles) in hexane was added to a solution of N,N,N',N'-tetramethylethylenediamine (TMEDA, 2 moles) in cyclohexane at a temperature of -8 to 0°C. When addition was complete, a 4.5M solution of thiophenol (1 mole) in cyclohexane was added and the temperature allowed to rise to 40-50°C. When addition was complete, the mixture was stirred

overnight at room temperature. A 4.5M solution of benzonitrile (1 mole) in cyclohexane was then added over 1 hour at a temperature of 15-20°C. When addition was complete, the mixture was heated at 40°C for 4 hours, then stirred at room temperature for 72 hours and quenched with water. The resulting organic phase was extracted with 1N sodium hydroxide and the combined extracts heated at 75°C for 2.5 hours, then cooled to room temperature, acidified to pH 1 using conc. HCl and extracted four times with toluene. The combined extracts were dried and evaporated in vacuo to give a red oil which was taken up in SD3A and stirred at room temperature for 16 hours. The resulting precipitate was filtered off and washed with SD3A to give the desired product as a white solid (61% yield).

(i) (R)-3-Ethyl-3-butyl-5-phenyl-2,3-dihydrobenzothiazepine

The solution from step (g) (1.05 moles) was added to a suspension of the product from step (h) (1 mole) in 2,6-lutidine (50ml) at a temperature of about 25°C. When addition was complete, the mixture was stirred at room temperature for 1.5 hours, then conc. HCl (6.3ml) added. When addition was complete, the mixture was azeotroped for 3 hours, then stirred at room temperature overnight and evaporated in vacuo. The residue was taken up in 5% w/v aqu. NaHCO₃ and the solution extracted twice with ethyl acetate. The combined extracts were washed with brine, dried and evaporated in vacuo. The residue was chromatographed in silica gel using 95:5 hexane:ethyl acetate as eluant to give the desired product as a red-orange oil (77% yield).

(j) (RR,RS)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine

A 1M solution of diborane in THF (63ml) was added to a solution of the product from step (i) (0.9 molar equivalents) in THF (100ml) at a temperature of about 1°C. When addition was

complete, the mixture was stirred overnight at room temperature, then cooled to about 0°C and 50% v/v HCl (40ml) added. When addition was complete, the mixture was stirred at room temperature for 1 hour, then concentrated in vacuo to remove the THF. Water (25ml) was added to the remaining aqueous phase, the pH adjusted to 8 using 12% w/v aqu. NaOH and the solution extracted with ethyl acetate. The combined extracts were dried and evaporated in vacuo to give the desired product as a red-orange oil comprising cis and trans isomers (100% yield).

(k) (RR,RS)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide

A suspension of the product from step (j) (0.33 molar equivalents) in trifluoroacetic acid (25ml) was added to a solution of 30% aqu. H₂O₂ (10.2ml) in trifluoroacetic acid (20ml) at a temperature of about 0°C. When addition was complete, the mixture was stirred overnight at room temperature, then poured into water (200ml) to give a waxy solid which was separated and taken up in 1N aqu. NaOH. The solution was heated to 40°C, then cooled and extracted with ethyl acetate. The combined extracts were washed with 1N aqu. NaOH, dried and evaporated in vacuo to give an oil comprising the cis and trans isomers (84% yield).

(l) (-)-(RR)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide

A solution of (-)-di-p-toluoyl-L-tartaric acid (1 mole) in diethyl ether (20ml) was added to a solution of the product from step (k) (1 mole) in diethyl ether (20ml). When addition was complete, the mixture was stirred at room temperature for 2 hours and the resulting crystals filtered off, washed with diethyl ether and dried to give the (RR)-tartrate salt which was neutralised with 1N aqu. NaOH and extracted with ethyl acetate. The combined extracts were dried and evaporated in vacuo to give

an oil which crystallised from hot hexanes to give the desired product as a white solid (58% yield). The mp, elemental analysis and ¹H NMR of the product were in agreement with those obtained by the alternative synthesis.

Preparation of (-)-(RR)-3-butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide hydrochloride

The product from Synthetic Example 1 (0.95g) was taken up in ether (75ml), 10M ethereal HCl (50ml) added and the mixture stood for 3 hours. The resulting precipitate was filtered off and dried to give the desired product as a white solid (0.86g), mp 184-188°C.

Analysis: Calcd. C 64.02; H 7.16; N 3.56; S 8.14

Found: C 64.09; H 7.16; N 3.01; S 8.21

¹H NMR (DMSO-d₆), δ: 0.81-0.91 (6H, m, CH₃); 1.00-1.04 (1H, m, CH₂); 1.29 (3H, b, CH₂); 1.92-2.00 (3H, b, CH₂); 2.50-2.51 (3H, b, CH₂ + NH₂); 3.40-4.80 (4H, b, CH₂SO₂); 6.20 (1H, b, CH); 6.83 (1H, b, Ar-H); 7.56-7.70 (7H, b, Ar-H); 8.10 (1H, b, Ar-H)

Synthetic Examples 2 - 64

Each of the following compounds of formula (I) was prepared by a method analogous to that of Synthetic Example 1 or by one of the other synthetic routes described herein. In all cases, ¹H NMR and elemental analysis were consistent with the proposed structure.

- 2) (+)-Trans-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide, mp 98-100°C;
- 3) (-)-Trans-3-Methyl-3-propyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide, mp 129-130°C;

- 4) 3-Ethyl-3-methyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine, mp 124-125°C;
- 5) (+)-3,3-Diethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide, mp 100-102°C;
- 6) 3-Butyl-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1,4-benzothiazepine 1,1-dioxide, mp 103-104°C;
- 7) 3-Methyl-3-propyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide, mp 120-121°C;
- 8) 3,3-Diethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide, mp 115-116°C;
- 9) (+)-Trans-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide, mp 101°C;
- 10) (+)-Trans-2,3,4,5-Tetrahydro-3-methyl-5-phenyl-3-propyl-1,4-benzothiazepine 1,1-dioxide, mp 129-130°C;
- 11) (-)-3,3-Diethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide, mp 101-103°C;
- 12) 3-Ethyl-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1,4-benzothiazepine, mp 110-112°C;
- 13) 3-Ethyl-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1,4-benzothiazepine hydrochloride 0.25H₂O, mp 162-164°C (eff.);
- 14) 3-Ethyl-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1,4-benzothiazepine 1,1-dioxide, mp 128-129°C;
- 15) 3,3-Diethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine hydrochloride, mp 211-214°C;

- 16) (+-)-2,3,4,5-Tetrahydro-3-methyl-5-phenyl-3-propyl-1,4-benzothiazepine, mp 101-103°C;
- 17) 2,3,4,5-Tetrahydro-3-methyl-5-phenyl-3-propyl-1,4-benzothiazepine, mp 72-74°C;
- 18) 3-Ethyl-2,3,4,5-tetrahydro-5-phenyl-3-propyl-1,4-benzothiazepine hydrochloride 0.25H₂O, mp 205-207°C;
- 19) 3-Ethyl-2,3,4,5-tetrahydro-5-phenyl-3-propyl-1,4-benzothiazepine 1,1-dioxide 0.25H₂O, mp 115-118°C;
- 20) 2,3,4,5-Tetrahydro-5-phenyl-3,3-dipropyl-1,4-benzothiazepine hydrochloride, 209-211°C;
- 21) 3-Ethyl-2,3,4,5-tetrahydro-5-phenyl-3-propyl-1,4-benzothiazepine 1,1-dioxide hydrochloride 0.33H₂O, 206-209°C;
- 22) 2,3,4,5-Tetrahydro-5-phenyl-3,3-dipropyl-1,4-benzothiazepine 1,1-dioxide, mp 104-106°C;
- 23) 3,3-Dibutyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine hydrochloride, mp 209-212°C;
- 24) 3-Butyl-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1,4-benzothiazepine hydrochloride, mp 203-205°C;
- 25) 3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine hydrochloride, mp 205-207°C;
- 26) 3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide hydrochloride, mp 209-212°C;
- 27) 2,3,4,5-Tetrahydro-3-methyl-3-pentyl-5-phenyl-1,4-benzothiazepine maleate, mp 182-183°C;

- 28) 3-Ethyl-2,3,4,5-tetrahydro-5-phenyl-3-propyl-1,4-benzothiazepine hydrochloride, mp 198-200°C;
- 29) (+)-Cis-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-7-methyl-5-phenyl-1,4-benzothiazepine 1,1-dioxide, mp 138-140°C;
- 30) (+)-Cis-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-7-methoxy-5-phenyl-1,4-benzothiazepine, light yellow oil;
- 31) (+)-Trans-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-7-methoxy-5-phenyl-1,4-benzothiazepine, light yellow oil;
- 32) (+)-Cis-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-7-methoxy-5-phenyl-1,4-benzothiazepine 1,1-dioxide, mp 113-115°C;
- 33) (+)-Cis-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-7-methoxy-5-phenyl-1,4-benzothiazepine 1-oxide, mp 103-105°C;
- 34) (+)-Trans-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-7-methoxy-5-phenyl-1,4-benzothiazepine 1,1-dioxide hydrochloride, mp 199-201°C;
- 35) (+)-Trans-3-Butyl-3-ethyl-5-phenyl-2,3,4,5-tetrahydro-1,4-benzothiazepine 1-oxide, mp 98-101°C;
- 36) (+)-Trans-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1-oxide, mp 133-136°C;
- 37) (+)-Cis-7-Chloro-3-butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 0.4 toluene, light yellow oil;
- 38) (+)-Trans-7-Chloro-3-butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 0.3 toluene, light yellow oil;
- 39) (+)-Trans-3-Butyl-7-Chloro-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide, mp 100-102°C;

40) (++)-Trans-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-(4-methoxyphenyl)-1,4-benzothiazepine 1,1-dioxide hydrochloride, mp 194-196°C;

41) (++)-Trans-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-(4-tolyl)-1,4-benzothiazepine 1,1-dioxide hydrochloride, mp 204-206°C;

42) (++)-Cis-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-(4-tolyl)-1,4-benzothiazepine 1,1-dioxide, mp 155-156C;

43) (++)-Cis-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-(4-methoxyphenyl)-1,4-benzothiazepine, mp 75-77°C;

44) (++)-Cis-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-(4-methoxyphenyl)-1,4-benzothiazepine 1,1-dioxide, mp 109-111°C;

45) (++)-Cis-3-Butyl-3-ethyl-5-(4-fluorophenyl)-2,3,4,5-tetrahydro-1,4-benzothiazepine, mp 76-78°C;

46) (++)-Trans-3-Butyl-5-(3,4-dichlorophenyl)-3-ethyl-2,3,4,5-tetrahydro-1,4-benzothiazepine, mp 98-100°C;

47) (++)-Trans-3-Butyl-5-(4-chlorophenyl)-3-ethyl-2,3,4,5-tetrahydro-1,4-benzothiazepine 1,1-dioxide hydrochloride 0.3 H₂O, mp 178-180°C;

48) (++)-Cis-3-Butyl-5-(4-chlorophenyl)-5-ethyl-2,3,4,5-tetrahydro-1,4-benzothiazepine 1,1-dioxide hydrochloride, mp 186-188°C;

49) Trans-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-(3-nitrophenyl)-1,4-benzothiazepine 1,1-dioxide, mp 139-142°C;

50) Trans-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-(4-nitrophenyl)-1,4-benzothiazepine 1,1-dioxide, mp 139-142°C;

- 51) (+)-Trans-5-(4-Benzylxyphenyl)-3-butyl-3-ethyl-2,3,4,5-tetrahydro-1,4-benzothiazepine 1,1-dioxide, mp 94-95°C;
- 52) (+)-Cis-5-(4-Benzylxyphenyl)-3-butyl-3-ethyl-2,3,4,5-tetrahydro-1,4-benzothiazepine 1,1-dioxide, mp 137-138°C;
- 53) (+)-Trans-5-(4-Benzylxyphenyl)-3-butyl-3-ethyl-2,3,4,5-tetrahydro-1,4-benzothiazepine, mp 97-98°C;
- 54) (+)-Trans-3-[4-(3-Butyl-3-ethyl-2,3,4,5-tetrahydro-1,4-benzothiazepin-5-yl)phenoxy]propanesulphonic acid 1,1-dioxide, mp 270°C (dec.);
- 55) (+)-Trans-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-(2-fluorophenyl)-1,4-benzothiazepine 1,1-dioxide hydrochloride, mp 194-196°C;
- 56) (+)-Trans-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-(3-fluorophenyl)-1,4-benzothiazepine 1,1-dioxide, mp 143-145°C;
- 57) (+)-Cis-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-(4-pyridyl)-1,4-benzothiazepine 1,1-dioxide, mp 121-123°C;
- 58) (+)-Trans-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-(4-pyridyl)-1,4-benzothiazepine 1,1-dioxide, mp 110-111°C;
- 59) (+)-Cis-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-(4-trifluoromethyl-phenyl)-1,4-benzothiazepine 1,1-dioxide, mp 64-65°C;
- 60) (+)-Trans-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-(3-trifluoromethylphenyl)-1,4-benzothiazepine 1,1-dioxide, mp 110-112°C;
- 61) (+)-Trans-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-(3,4-difluorophenyl)-1,4-benzothiazepine 1,1-dioxide, mp 205-215°C;

62) (+)-Trans-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-(2,4-difluoro-phenyl)-1,4-benzothiazepine 1,1-dioxide, mp 97-99°C;

63) (+)-Trans-3-isopentyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide, mp 86-87°C; and

64) (+)-Cis-3-isopentyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide, mp 123-125°C..

Pharmaceutical Composition Examples

In the following Examples, the active compound can be any compound of formula (I) and/or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof. The active compound is preferably (-)-(RR)-3-butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine or one of the compounds of Synthetic Examples 2 to 64.

(i) Tablet compositions

The following compositions A and B can be prepared by wet granulation of ingredients (a) to (c) and (a) to (d) with a solution of povidone, followed by addition of the magnesium stearate and compression.

Composition A

	<u>mg/tablet</u>	<u>mg/tablet</u>
(a) Active ingredient	250	250
(b) Lactose B.P.	210	26
(c) Sodium Starch Glycollate	20	12
(d) Povidone B.P.	15	9
(e) Magnesium Stearate	<u>5</u>	<u>3</u>
	500	300

Composition B

	<u>mg/tablet</u>	<u>mg/tablet</u>
(a) Active ingredient	250	250

(b)	Lactose	150	150	-
(c)	Avicel PH 101		60	26
(d)	Sodium Starch Glycollate		20	12
(e)	Povidone B.P.		15	9
(f)	Magnesium Stearate		<u>5</u>	<u>3</u>
			500	300

Composition C

	<u>mg/tablet</u>
Active ingredient	100
Lactose	200
Starch	50
Povidone	5
Magnesium Stearate	<u>4</u>
	359

The following compositions D and E can be prepared by direct compression of the admixed ingredients. The lactose used in composition E is of the direct compression type.

Composition D

	<u>mg/tablet</u>
Active ingredient	250
Magnesium Stearate	4
Pregelatinised Starch NF15	<u>146</u>
	400

Composition E

	<u>mg/tablet</u>
Active ingredient	250
Magnesium Stearate	5
Lactose	145
Avicel	<u>100</u>
	500

Composition F (Controlled release composition)

	<u>mg/tablet</u>
(a) Active ingredient	500
(b) Hydroxypropylmethylcellulose (Methocel K4M Premium)	112
(c) Lactose B.P.	53
(d) Povidone B.P.C.	28
(e) Magnesium Stearate	<u>7</u>
	700

The composition can be prepared by wet granulation of ingredients (a) to (c) with a solution of povidone, followed by addition of the magnesium stearate and compression.

Composition G (Enteric-coated tablet)

Enteric-coated tablets of Composition G can be prepared by coating the tablets with 25mg/tablet of an enteric polymer such as cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropylmethylcellulose phthalate, or anionic polymers of methacrylic acid and methacrylic acid methyl ester (Eudragit L). Except for Eudragit L, these polymers should also include 10% (by weight of the quantity of polymer used) of a plasticizer to prevent membrane cracking during application or on storage. Suitable plasticizers include diethyl phthalate, tributyl citrate and triacetin.

Composition H (Enteric-coated controlled release tablet)

Enteric-coated tablets of Composition F can be prepared by coating the tablets with 50mg/tablet of an enteric polymer such as cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropylmethylcellulose phthalate, or anionic polymers of methacrylic acid and methacrylic acid methyl ester (Eudragit L). Except for Eudragit L,

these polymers should also include 10% (by weight of the quantity of polymer used) of a plasticizer to prevent membrane cracking during application or on storage. Suitable plasticizers include diethyl phthalate, tributyl citrate and triacetin.

(ii) Capsule compositions

Composition A

Capsules can be prepared by admixing the ingredients of Composition D above and filling two-part hard gelatin capsules with the resulting mixture. Composition B (infra) may be prepared in a similar manner.

Composition B

	<u>mg/capsule</u>
(a) Active ingredient	250
(b) Lactose B.P.	143
(c) Sodium Starch Glycollate	25
(d) Magnesium Stearate	<u>2</u>
	420

Composition C

	<u>mg/capsule</u>
(a) Active ingredient	250
(b) Macrogol 4000 BP	<u>350</u>
	600

Capsules can be prepared by melting the Macrogol 4000 BP, dispersing the active ingredient in the melt and filling two-part hard gelatin capsules therewith.

Composition D

	<u>mg/capsule</u>
Active ingredient	250
Lecithin	100
Arachis Oil	<u>100</u>
	450

Capsules can be prepared by dispersing the active ingredient in the lecithin and arachis oil and filling soft, elastic gelatin capsules with the dispersion.

Composition E (Controlled release capsule)

	<u>mg/capsule</u>
(a) Active ingredient	250
(b) Microcrystalline Cellulose	125
(c) Lactose BP	125
(d) Ethyl Cellulose	<u>13</u>
	513

The controlled release capsule composition can be prepared by extruding mixed ingredients (a) to (c) using an extruder, then spheronising and drying the extrudate. The dried pellets are coated with a release controlling membrane (d) and filled into two-part, hard gelatin capsules.

Composition F (Enteric capsule)

	<u>mg/capsule</u>
(a) Active ingredient	250
(b) Microcrystalline Cellulose	125
(c) Lactose BP	125
(d) Cellulose Acetate Phthalate	50
(e) Diethyl Phthalate	<u>5</u>
	555

The enteric capsule composition can be prepared by extruding mixed ingredients (a) to (c) using an extruder, then spheronising and drying the extrudate. The dried pellets are coated with an enteric membrane (d) containing a plasticizer (e) and filled into two-part, hard gelatin capsules.

Composition G (Enteric-coated controlled release capsule)

Enteric capsules of Composition E can be prepared by coating the controlled-release pellets with 50mg/capsule of an enteric polymer such as cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropylmethylcellulose phthalate, or anionic polymers of methacrylic acid and methacrylic acid methyl ester (Eudragit L). Except for Eudragit L, these polymers should also include 10% (by weight of the quantity of polymer used) of a plasticizer to prevent membrane cracking during application or on storage. Suitable plasticizers include diethyl phthalate, tributyl citrate and triacetin.

(iii) Intravenous injection composition

Active ingredient	0.200g
Sterile, pyrogen-free phosphate buffer (pH 9.0)	to 10 ml

The active ingredient is dissolved in most of the phosphate buffer at 35-40°C, then made up to volume and filtered through a sterile micropore filter into sterile 10 ml glass vials (Type 1) which are sealed with sterile closures and overseals.

(iv) Intramuscular injection composition

Active ingredient	0.20 g
Benzyl Alcohol	0.10 g
Glycofuro 75	1.45 g
Water for Injection q.s.	to 3.00 ml

The active ingredient is dissolved in the glycofurool. The benzyl alcohol is then added and dissolved, and water added to 3 ml. The mixture is then filtered through a sterile micropore filter and sealed in sterile 3 ml glass vials (Type 1).

(v) Syrup composition

Active ingredient	0.25g
Sorbitol Solution	1.50g
Glycerol	1.00g
Sodium Benzoate	0.005g
Flavour	0.0125ml
Purified Water q.s. to	5.0ml

The sodium benzoate is dissolved in a portion of the purified water and the sorbitol solution added. The active ingredient is added and dissolved. The resulting solution is mixed with the glycerol and then made up to the required volume with the purified water.

(vi) Suppository composition

mg/suppository

Active ingredient	250
Hard Fat, BP (Witepsol H15 - Dynamit NoBel)	1770
	2020

One-fifth of the Witepsol H15 is melted in a steam-jacketed pan at 45°C maximum. The active ingredient is sifted through a 200µm sieve and added to the molten base with mixing, using a Silverson fitted with a cutting head, until a smooth dispersion is achieved. Maintaining the mixture at 45°C, the remaining Witepsol H15 is added to the suspension which is stirred to ensure a homogenous mix. The entire suspension is then passed through a 250µm stainless steel screen and, with continuous stirring, allowed to cool to 40°C. At a temperature of 38-40°C, 2.02g aliquots of the mixture are filled into

suitable plastic moulds and the suppositories allowed to cool to room temperature.

(vii) Pessary composition

	<u>mg/pessary</u>
Active ingredient (63 μ m)	250
Anhydrous Dextrose	380
Potato Starch	363
Magnesium Stearate	<u>7</u>
	1000

The above ingredients are mixed directly and pessaries prepared by compression of the resulting mixture.

(viii) Transdermal composition

Active ingredient	200mg
Alcohol USP	0.1ml
Hydroxyethyl cellulose	

The active ingredient and alcohol USP are gelled with hydroxyethyl cellulose and packed in a transdermal device with a surface area of 10 cm².

Biological Assay

In vitro inhibition of bile acid uptake

Freshly prepared rat distal ileal brush border membrane vesicles (about 200mg vesicle protein) were incubated for 30 seconds at 24°C in an incubation mixture comprising 10 μ M ³H taurocholate, 100mM NaCl (or KCl) and 80mM mannitol in 20mM Hepes Tris pH 7.4. Each test compound was dissolved in ethanol (or water) and then diluted with incubation mixture to an ethanol concentration of not more than 1% v/v. The

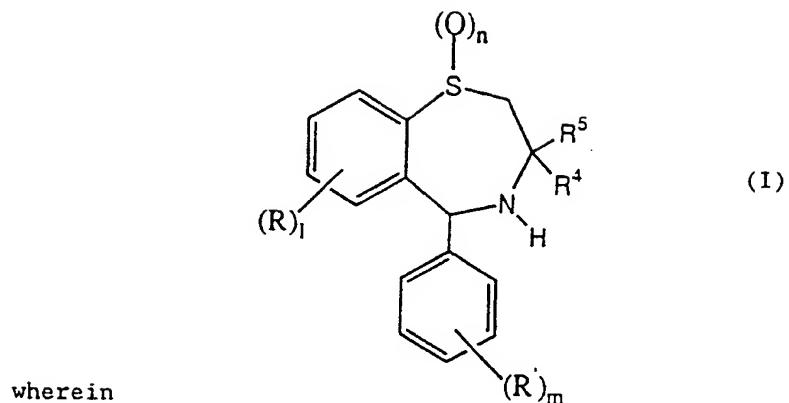
incubation was terminated by rapid dilution and filtration and the filter washed with an ice-cold isotonic sodium-free buffer.

The uptake of ^3H taurocholate was measured by the radioactivity remaining on the filter and converted to pmoles/mg vesicle protein. The active, ie sodium-dependent, uptake was obtained by subtracting the passive uptake measured in 100mM KCl from the total uptake measured in 100mM NaCl. The active uptake for each test compound was compared with a control active uptake and the results expressed at % inhibition of bile acid uptake.

For the compound of Synthetic Example 1, the % inhibition of bile acid uptake at concentrations of 10, 3, 1 and $0.3\mu\text{M}$ was 96, 85, 69 and 55% respectively.

CLAIMS

1. A compound of formula (I)



wherein

l is an integer of from 0 to 4;

m is an integer of from 0 to 5;

n is an integer of from 0 to 2;

R and R' are atoms or groups independently selected from halogen, nitro, phenylalkoxy, C_{1-4} alkoxy, C_{1-6} alkyl and $-O(CH_2)_pSO_3R''$ wherein p is an integer of from 1 to 4 and R'' is hydrogen or C_{1-6} alkyl, wherein said phenylalkoxy, alkoxy and alkyl groups are optionally substituted by one or more halogen atoms;

R^4 is a C_{1-6} straight alkyl group; and

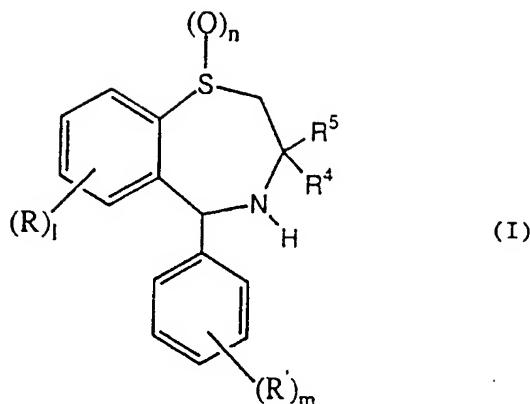
R^5 is a C_{2-6} straight alkyl group;

and salts, solvates and physiologically functional derivatives thereof.

2. A compound of formula (I) as claimed in Claim 1, wherein
n is 2;
 R^4 is methyl, ethyl, n-propyl, or n-butyl; and
 R^5 is ethyl, n-propyl, or n-butyl;
and salts, solvates and physiologically functional derivatives thereof.
3. A compound of formula (I) as claimed in Claim 2, which compound is in the trans configuration as herein defined, or a salt, solvate, or physiologically functional derivative thereof.
4. A compound of formula (I) as claimed in Claim 3, which compound is trans-3-butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide, or a salt, solvate, or physiologically functional derivative thereof.
5. The compound of formula (I) claimed in Claim 4, which compound is in the (RR)-, (SS)-, or (RR,SS)-form, or is a salt, solvate, or physiologically functional derivative of any thereof.
6. (-)-(RR)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide or a salt, solvate, or physiologically functional derivative thereof.
7. (-)-(RR)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide
8. (+-)-(RR,SS)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide or a salt, solvate, or physiologically functional derivative thereof.

9. (++)-(RR,SS)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-dioxide
10. A compound as claimed in any of Claims 1 to 7, or a physiologically acceptable salt, solvate, or physiologically functional derivative thereof, for use as a therapeutic agent.
11. A compound as claimed in any of Claims 1 to 7, or a physiologically acceptable salt, solvate, or physiologically functional derivative thereof, for use in the prophylaxis or treatment of a clinical condition for which a bile acid absorption inhibitor is indicated.
12. A compound as claimed in any of Claims 1 to 7, or a physiologically acceptable salt, solvate, or physiologically functional derivative thereof, for use in the prophylaxis or treatment of hyperlipidaemia.
13. A compound as claimed in any of Claims 1 to 7, or a physiologically acceptable salt, solvate, or physiologically functional derivative thereof, for use in the prophylaxis or treatment of atherosclerosis.
14. Use of a compound as claimed in any of Claims 1 to 7, or a physiologically acceptable salt, solvate, or physiologically functional derivative thereof, in the manufacture of a pharmaceutical composition for the prophylaxis or treatment of a clinical condition for which a bile acid absorption inhibitor is indicated.
15. Use of a compound as claimed in any of Claims 1 to 7, or a physiologically acceptable salt, solvate, or physiologically functional derivative thereof, in the manufacture of a pharmaceutical composition for the prophylaxis or treatment of hyperlipidaemia.

16. Use of a compound as claimed in any of Claims 1 to 7, or a physiologically acceptable salt, solvate, or physiologically functional derivative thereof, in the manufacture of a pharmaceutical composition for the prophylaxis or treatment of atherosclerosis.
17. A method for the prophylaxis or treatment of a clinical condition in a mammal for which a bile acid absorption inhibitor is indicated which comprises the administration to said mammal of an effective bile acid absorption inhibiting amount of a compound of formula (I) as claimed in any of Claims 1 to 7 or of a physiologically acceptable salt, solvate, or physiologically functional derivative thereof.
18. A method as claimed in Claim 15 for the prophylaxis or treatment of hyperlipidaemia.
19. A method as claimed in Claim 15 or 16 for the prophylaxis or treatment of atherosclerosis.
20. A method as claimed in any of Claims 15 to 17 wherein said mammal is a human.
21. A pharmaceutical composition comprising a compound of formula (I) as claimed in any of Claims 1 to 7 or a physiologically acceptable salt, solvate, or physiologically functional derivative thereof, at least one pharmaceutically acceptable carrier and, optionally, one or more other physiologically active agents.
22. A pharmaceutical composition as claimed in Claim 19 which is in the form of a tablet or capsule.
23. A process for the preparation of a compound of formula (I)



wherein

l is an integer of from 0 to 4;

m is an integer of from 0 to 5;

n is an integer of from 0 to 2;

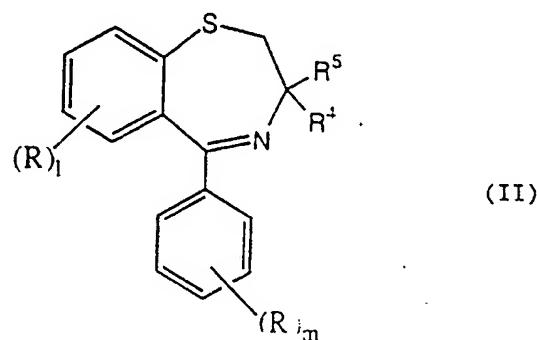
R and R' are atoms or groups independently selected from halogen, nitro, phenylalkoxy, C_{1-4} alkoxy, C_{1-6} alkyl and $-O(CH_2)_pSO_3R''$ wherein p is an integer of from 1 to 4 and R'' is hydrogen or C_{1-6} alkyl, wherein said phenylalkoxy, alkoxy and alkyl groups are optionally substituted by one or more halogen atoms;

R^4 is a C_{1-6} straight alkyl group; and

R^5 is a C_{2-6} straight alkyl group;

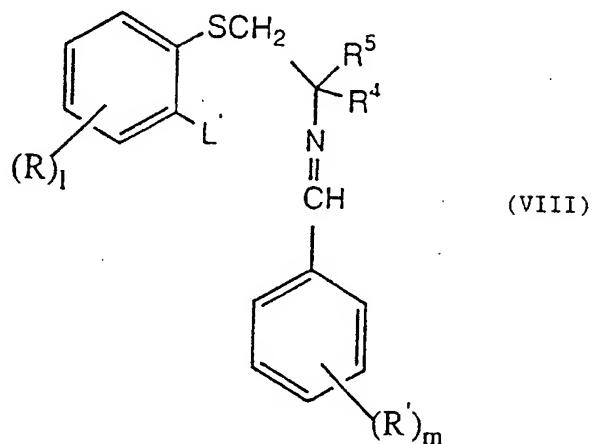
which comprises

(a) reducing the imine bond of a compound of formula (II)



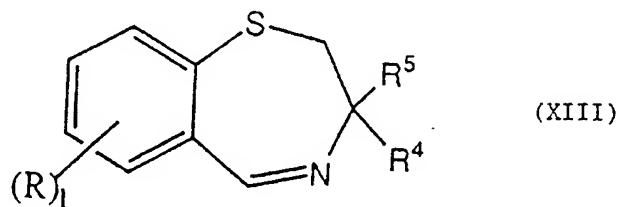
wherein l, m, R, R', R⁴ and R⁵ are as hereinbefore defined;

(b) cyclising a compound of formula (VIII)



wherein l, m, R, R', R⁴ and R⁵ are as hereinbefore defined and L' is halogen; or

(c) phenylating a compound of formula (XIII)



wherein l, R, R⁴ and R⁵ are as hereinbefore defined;

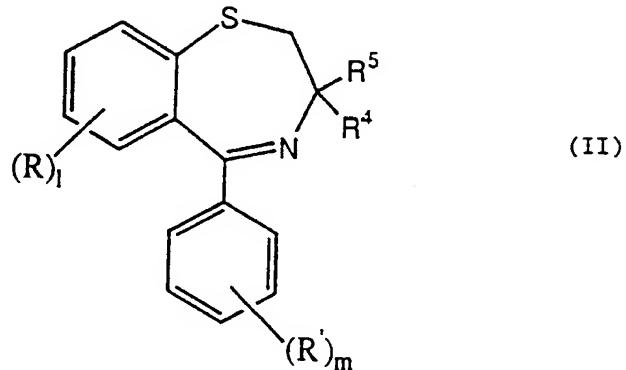
and optionally oxidising the compound of formula (I) so obtained to the corresponding compound wherein n = 1 or 2 followed by optional conversion to a salt, solvate, or physiologically functional derivative thereof.

24. A method of preparing a pharmaceutical composition which comprises

- (a) preparing a compound of formula (I) or a physiologically acceptable salt, solvate, or physiologically functional derivative thereof by a process as claimed in Claim 21; and
- (b) admixing the product from step (a) with at least one pharmaceutically acceptable carrier and, optionally, one or more other physiologically active agents.

25. A method as claimed in Claim 22 which comprises an additional step (c) wherein the admixture from step (b) is formed into a tablet or capsule.

26. A compound of formula (II)



wherein 1, m, R, R', R⁴ and R⁵ are as defined in Claim 1.

27. 3-Ethyl-3-butyl-5-phenyl-2,3-dihydrobenzothiazepine

28. (R)-3-Ethyl-3-butyl-5-phenyl-2,3-dihydrobenzothiazepine

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 93/00328

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)⁶

According to International Patent Classification (IPC) or to both National Classification and IPC
 Int.CI. 5 C07D281/10

II. FIELDS SEARCHED

Minimum Documentation Searched⁷

Classification System	Classification Symbols
Int.CI. 5	C07D

Documentation Searched other than Minimum Documentation
 to the Extent that such Documents are Included in the Fields Searched⁸

III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹

Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	US,A,3 362 962 (EARL R. NUTLEY ET AL.) 9 January 1968 cited in the application see the whole document -----	1,2, 10-16

¹⁰ Special categories of cited documents :¹⁰

- ^{"A"} document defining the general state of the art which is not considered to be of particular relevance
- ^{"E"} earlier document but published on or after the international filing date
- ^{"L"} document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- ^{"O"} document referring to an oral disclosure, use, exhibition or other means
- ^{"P"} document published prior to the international filing date but later than the priority date claimed

^{"T"} later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

^{"X"} document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

^{"Y"} document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

^{"&"} document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search 29 APRIL 1993	Date of Mailing of this International Search Report 13. 05. 93
International Searching Authority EUROPEAN PATENT OFFICE	Signature of Authorized Officer FRANCOIS J.C.

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.

GB 9300328
SA 70210

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 29/04/93

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-3362962		BE-A- 658798 CH-A- 494207 DE-A- 1545932 FR-M- 4916 FR-A- 1422569 GB-A- 1091182 NL-A- 6500817 US-A- 3503985 US-A- 3523974 US-A- 3530139 US-A- 3631089	26-07-65 31-07-70 08-01-70 26-07-65 31-03-70 11-08-70 22-09-70 28-12-71